Drug and Therapeutics Committee Training Course

Session 4: Assessing and Managing Drug Safety

Participant's Guide

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PURPOSE AND CONTENT

This session provides the participants with basic information about assessing and managing drug safety issues.

Objectives

After attending this session, participants will be able to—

- Describe the significance of adverse drugs reactions on health care systems
- Understand the principles of drug safety evaluation
- Discuss the evaluation of spontaneous case reports of adverse drug reactions
- Understand techniques for monitoring, evaluation, and prevention of adverse drug reactions

Preparation

Read Participant's Guide.

INTRODUCTION

Drugs have become one of the most essential components of health care systems worldwide. Drugs save lives. This indisputable fact makes rational selection, procurement, distribution, and rational use of drugs of paramount importance in health care.

Unfortunately, there are often shortcomings in the prescribing and taking of drugs. One very important concern is that of safety. Drugs are produced synthetically or from natural substances and most will exhibit some form of side effect or adverse drug reaction (ADR). These side effects or adverse reactions may be relatively mild or, in rare cases, serious and life threatening. This session discusses the problem, how to assess the true extent of the problem, and how to monitor and prevent drug-related safety problems.

KEY DEFINITIONS

Adverse Drug Reaction – The World Health Organization defines an adverse drug reaction as "any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function." An unexpected adverse drug reaction refers to a reaction, the nature or severity of which is not consistent with domestic labeling or market authorization, or expected from characteristics of the drug.

Side Effect—Expected, well-known reaction to a drug resulting in little or no change in patient management.

Causality—The probability that a particular drug or substance is responsible for an isolated effect or ADR.

DRUG SAFETY AND ADVERSE DRUG REACTIONS

Adverse drug reactions are unexpected, unintended, undesirable, or excessive responses to a drug that may be harmful to the patient. Side effects are known reactions to a drug and are typically listed in the drug's labeling.

The American Society of Health-System Pharmacists provides another definition of ADR. It describes an ADR as any unexpected, unintended, undesirable, or excessive response to a drug that—

- Requires discontinuing the drug
- Requires changing the drug
- Requires modifying the dose
- Necessitates admission to a hospital
- Prolongs stay in a health care facility
- Necessitates supportive treatment

- Significantly complicates diagnosis
- Negatively affects prognosis
- Results in temporary or permanent harm, disability, or death

(Source: ASHP Technical Bulletins)

Adverse drug reactions can be classified into two types:

Type A Reactions—These reactions are an exaggerated but otherwise normal pharmacological response to the effects of the drugs given in therapeutic dose. These reactions cause significant morbidity but are rarely severe. Examples of such reactions include—

- Pharmacodynamic (e.g., bronchospasm with beta-blocker administration)
- Toxic (e.g., absolute or relative overdosing of aminoglycosides)
- Withdrawal syndrome or rebound effect (e.g., spontaneous clonidine discontinuation)

Type B Reactions—These reactions are bizarre and unpredictable with no relation to dose and are often allergic in nature. They are often severe and cause high mortality. Examples of such reactions include—

- Drug-induced diseases (e.g., super-infection after antibiotic use)
- Allergic reactions (e.g., anaphylactic reaction to penicillin administration)
- Idiosyncratic reactions (irreversible aplastic anemia caused by chloramphenicol)

Adverse events as a result of drug interactions may be manifested in all degrees of severity and type including—

- Reduced absorption of tetracyclines if administered with calcium
- Phenytoin toxicity when administered in conjunction with fluconazole
- Digoxin toxicity when administered with furosemide

Adverse drug reactions are a serious problem with increasing incidence as more drugs become available and more people become exposed to them. In the United States, a recent review of prospective studies showed that hospitalized patients in 1994 had 2.2 million adverse drug reactions (6.7 percent incidence), which resulted in 106,000 fatalities (Lazarou et al. 1998[*]). This would place adverse drug reactions among the top 10 causes of death in the United States. These statistics become even more significant when you consider that they do not include errors of administration, which would only increase the total incidence of morbidity and mortality related to drug use.

It is difficult to extrapolate these figures to other countries, but it is reasonable to assume that all countries have a significant problem in terms of adverse drug reactions and subsequent increase

[*] Lazarou, J, Pomeranz, BH and Corey, PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998 April 15; 279(15): 1200–5.

in morbidity and mortality as a direct result. It is therefore appropriate to address these issues carefully and comprehensively in order to provide for better patient care.
Most drugs undergo a significant amount of testing and evaluation before marketing to ensure the product is not only effective but also safe. There are no drugs on the market today that are free of side effects or adverse reactions. Many products have an extremely low incidence of side effects, such as cromolyn inhalation products. Others, such as antineoplastic drugs, exhibit extremely high incidence of adverse reactions, many resulting in death. A very close monitoring and evaluation of most drugs is necessary in order to prevent more serious side effects from occurring.

Marketing drugs requires many clinical trials to establish efficacy, safety, quality, and cost-benefit. Clinical trials will determine the most common adverse events, those with an occurrence of 1 percent or more during the development of a new drug. Adverse events that are less common (< 1 percent incidence) may not be identified in these premarketing studies and will rely on postmarketing clinical studies and reporting by physicians, pharmacists, and patients for identification of these uncommon events.

Every drug has a risk-benefit ratio. Depending on the patient's condition being treated, ancillary problems, age, and many other parameters, the patient can be expected to obtain both a measurable benefit and experience a certain degree of risk. Careful evaluation by the practitioner before use of the drug is always necessary to obtain the most beneficial effect from the drug, minimize adverse drug reactions, and obtain value for the cost of the product. This can be accomplished by careful review of the patient's history, evaluation of current health status, and the avoidance of drugs that may have a higher incidence of adverse drug reactions in the patient.

PREMARKETING SAFETY EVALUATIONS

Premarket testing is extensive for most drugs that are produced in Japan, North America, and Europe. Typically a new drug would have the following evaluation before being marketed:

- Animal studies
    - Acute and chronic toxicity—Studies are conducted for varying periods of time, from 14 days to over one year in two or more species of test animal.
    - Mutagenicity and carcinogenicity—A battery of mutagenicity tests evaluates the potential for genetic problems; testing is performed in at least two animal species for a period of two years. Testing is done only if the drug is intended for chronic use.
    - Teratogenicity—Tests are performed on animal species to assess ability to reproduce and have a normal offspring free of birth defects; the ability of the offspring to grow normally and reproduce is also tested extensively.

- Human studies

    - Clinical trials—Study of the effects of drugs on humans under rigorously controlled trials. Most clinical trials will assess safety. The number of clinical trials performed before a drug is approved averages 68; the average number of patients used in these trials is approximately 4,000.

        - Phase I—Single dose studies, using low doses of the drug. Subsequently larger doses and multiple sequences are evaluated.

        - Phase II—Efficacy is the primary objective of phase II trials, but safety is also continuously monitored and evaluated.

        - Phase III—Evaluations of safety in groups of patients with the disease, including those who are elderly, have ancillary diseases, use other drugs, and have compromised renal and liver function.

        - Phase IV—Postmarketing surveillance and clinical trials.

Premarketing safety evaluations have two significant drawbacks—

- Underidentification of adverse drug reactions—Low-incidence ADRs, those reactions with an incidence less than 1 percent, are frequently not identified.

- Overidentification of ADRs—Many adverse drug reactions that are identified in preclinical studies are not proven to be causal, but are still listed in the product literature as potentially causing the ADR. This provides some measure of legal protection for the pharmaceutical company but is misleading to practitioners, as many of these reactions are not definitely proven.

POSTMARKET SURVEILLANCE OF ADVERSE DRUG REACTIONS

After drugs have been released on the market, manufacturers are responsible for postmarketing surveillance of these products. It is not possible to have identified all of the safety-related problems that may exist with a new drug during premarket testing and evaluation.

Drugs released onto the open market will be used not only by more people, but also by older and sicker people, different ethnic groups, pregnant women, and children and under many different dose regimens (not necessarily the correct and approved dose). These circumstances inevitably lead to a potential for more adverse drug reactions.

Spontaneous Reports

Spontaneous reports are reports of an adverse drug reaction by a physician, pharmacist, or patient. In many countries these reports are sent to regulatory agencies or the manufacturer of the drug.

Spontaneous reports have been shown to identify new adverse drug reactions more often than any other method. Consequently, this reporting and identification method has held the most significance for manufacturers over the past 10 years. These reports have the advantage of being available immediately as new products are released and throughout the market life of the drug. A spontaneous report of a reaction describes the reaction that has occurred, but need only have the suspicion that an adverse event may be related to the use of the drug. All serious reactions should be reported, i.e., those that lead to death, hospitalization, significant or permanent disability, or to congenital abnormality or that require medical or surgical intervention. Many less serious reactions should also be reported, especially new and unusual reactions.
The greatest limitation of spontaneous reports is that there is a significant underreporting of adverse reactions. Another limitation of spontaneous reporting is a high incidence of false positives in the reporting of adverse events. It is very difficult for many practitioners to accurately assess and determine causality of an adverse drug reaction, and there is a high incidence of erroneous reports by physicians and pharmacists. Patients are also a source for the reporting of an adverse event and the quality of these reports is frequently unreliable.

Multinational drug manufacturers employ a worldwide system of collection, aggregation, and evaluation of ADRs. Data are collected by telephone calls, letters, and literature reviews, and through regulatory authorities. The companies report serious ADRs to regulatory organizations on a regular basis.

Clinical Studies

Postmarketing clinical studies are frequently done to assess efficacy and safety. The two methods used are randomized control trials and observational studies.

Randomized Controlled Trials

Randomized controlled trials (RCT) are valuable tools for uncovering adverse events in preclinical studies. For postmarketing discovery of events, however, the RCT is frequently disappointing. The elimination of confounding factors is excellent in this setting, but there is generally insufficient power in the trial to discover an event that was not already observed in premarketing studies. Randomized controlled trials are also expensive and difficult to manage.

Observational Studies

Large databases from national health programs and from large health maintenance organizations in North America and Europe provide valuable information concerning drug safety. These databases (with millions of entries) are acceptable for providing information in a case-control or cohort study. A cohort study identifies two groups of patients: one that is exposed to the study drug and another that is not treated or receives an alternate form of therapy.

Drug manufacturers frequently set up and sponsor large cohort studies to assess safety issues that have arisen after a drug has come to market. These studies allow for the control of potential confounders, bias, and chance to a greater extent than spontaneous reports or case reports, but still are susceptible to these factors. Cohort studies are helpful in attempting to assign causality when spontaneous reports indicate a potential for a drug to cause an adverse event. These types of studies can be unsuccessful because the numbers of patients selected will often be insufficient to provide statistical significance for rare ADRs.

Published Case Reports

Published case reports can be found in medical and pharmaceutical journals and describe the occurrence of a significant adverse drug reaction. These reports can have drawbacks as they may not be well documented and have a long lead-time from the identification of the event to publication in a journal. These reports are also published at the discretion of editors and publishers.

Meta-analysis of Clinical Studies

Meta-analysis of published studies is another valuable method to obtain information concerning the incidence and prevalence of adverse drug reactions. A meta-analysis takes two or more single studies concerning a particular drug or reaction and combines them to provide more power for the statistical analysis. Individual reports may not have the statistical power to make conclusions concerning an adverse drug reaction, but combining several reports will provide the appropriate numbers when one study showed only an insignificant effect.

Corrective Action Concerning Postmarket Surveillance

The surveillance systems currently in place inevitably obtain important new information about drug safety and adverse drug reactions. This information is placed in a database and analyzed by manufacturers or regulatory agencies. When it becomes apparent that a new safety concern has been detected, appropriate action is taken. The response is usually in three forms—

- Letters—These are sent to physicians and pharmacists describing a concern about a particular drug. The letter may provide specifics about the new safety concern and how it may impact present patients on the drug and future prescribing. It may be only a warning

of possible safety concerns that have been detected and may recommend a continued vigilance in prescribing and dispensing the drug.

- Package insert revisions—When safety concerns become significant, then it becomes necessary for manufacturers to re-label the product. This requires changing the official labeling and changing the package insert to reflect the new safety concern. Regulatory officials typically approve the change.

- Drug recalls—Surveillance systems are intended to monitor drug safety. It is the responsibility of manufacturers and regulatory authorities to monitor and assess the postmarket surveillance reports. When thresholds for acceptable ADR incidence (or for quality issues) are exceeded and the risk of side effects outweighs the benefits, then it may become necessary to withdraw the drug from the market. Drugs recalls can be voluntary or imposed by regulatory authorities. This action is rarely necessary.

DETERMINING CAUSALITY OF AN ADR

Causality of an ADR is a critical issue that requires the linking of any adverse event to a drug or other cause. When a specific symptom occurs following the administration of a drug, it does not mean that the drug is responsible. There are numerous other possibilities that may be responsible for the adverse event. Also, you cannot conclude that, because a particular drug has not been taken for some time and an adverse event occurs, the time interval eliminates the drug as a cause of the event.

The following are associations that support causation linking a drug and suspected adverse reaction (adapted from Gehlbach 1993[*]):

- Strength of the association
- Consistency of the observed evidence
- Temporality of the relationship
- Dose-response relationship
- Confounding factors

Strength of Association

If the odds are known and are very high for an observed event, e.g., gastrointestinal upset with aspirin, then the case is strengthened for causation.

[*] Gehlbach, SH. *Interpreting the Medical Literature.* Third edition. New York: McGraw-Hill, Inc. 1993:224–8.

Consistency of the Observed Evidence

When there is an association between a drug and an adverse reaction that has been demonstrated consistently over years of clinical practice, causality becomes more likely.

Temporality of the Relationship

The closer the relationship of the administration of the drug and the occurrence of the ADR, the more likely that the drug may be the actual cause of the reaction. This is not always true as some adverse events may occur several weeks after the administration of the offending drug.

Dose-Response Relationship

Frequently, adverse events occur in relation to the dose being administered. The higher the dose of the drug, the more likely an ADR is a result of the administered agent. A lower dose has a corresponding decrease in the ADR. However, this is not always true as very low doses of some drugs, e.g., penicillin, can elicit serious anaphylactic responses.

Causality Assessment of Suspected Adverse Reactions

Certain causality is where a clinical event (including laboratory test abnormality) occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. A plausible (expected) clinical response to withdrawal of the drug must be demonstrated and, if possible, the clinical response to restarting the drug should also be demonstrated.

Probable or likely causality is where a clinical event occurs with a reasonable time sequence to drug administration, and it is unlikely to be due to any concurrent disease or other drug administration.

Possible or likely causality is where a clinical event occurs with a reasonable time sequence to drug administration, but which could be explained by concurrent disease or other drug administration. Information on drug withdrawal may be lacking or unclear.

Confounding Factors

The minimization of confounding factors is important in determining causality. Confounding factors such as the administration of others drugs, food, and beverages can account for observed events. The existence of concurrent diseases and infections can also cause certain observed effects, making it difficult to distinguish them from the suspected drug. Environmental factors, such as air pollutants, weather conditions, and exposure to allergens, may also play a role.

IMPLICATIONS FOR THE DTC

Assessment of Spontaneous Reports from Hospitals and Clinics

The DTC should become involved in the processing and analysis of spontaneous case reports arising from patients and medical providers. These spontaneous reports from practitioners may be difficult to interpret and to assign causality. The following are frequent problems that arise with adverse drug reactions reported at a hospital or primary care clinic:

- A particular generic drug causes an adverse drug reaction where the brand name product does not.
- A brand name product is alleged to cause more side effects than another branded product.
- An antibiotic suspension causes a reaction and it is unclear if responsibility lies with the antibiotic or one of the components of the suspension, i.e., dyes or other excipient in the suspension.
- An injectable product causes a reaction and it is unclear if the causative agent is the active ingredient or related to a preservative or other agent in the solvent.
- A patient is on several drugs when a new adverse event is reported; assigning causality becomes problematic because any number of the drugs may be the cause.
- The patient has co-morbid conditions that may have a bearing on the drug and suspected ADR.

The following are the steps necessary to evaluate an ADR observed in the hospital or primary care clinic:

1. Identify and check the clinical syndrome described for the ADR.
2. Assess primary literature and other references for information concerning the incidence and probability of the reaction occurring for this particular patient.
3. Obtain a detailed history of the patient including current health status, current drug therapy, and past medical history. Utilize an adverse drug reaction reporting form to organize reporting. See Appendix 1 for an example of a report form.
4. Utilize the Naranjo Algorithm (or other system) for assessing the reaction. This algorithm will assist the practitioner in determining the probability that an adverse drug reaction has actually occurred from the suspected drug. The algorithm asks a number of questions about the adverse event and provides a numerical rating for the importance of each question. The scores for all items are added to give a probability of causality of the adverse event. See Appendix 2 for an example of this algorithm.

5. Classify results of reaction:

    - Severe—Fatal or life-threatening
    - Moderate—Requires antidote, medical procedure, or hospitalization
    - Mild—Symptoms are obvious and require only the discontinuation of drug therapy
    - Incidental—Very mild symptoms; patient is given the option to continue or discontinue medication

6. Evaluate the quality of the product from the manufacturer to rule out any adverse event occurring from a poor-quality product. This investigation should include the possibility of drug counterfeiting and overt contamination of the product.

7. With information obtained through this process, make a definitive decision based upon the facts as presented. All significant adverse drug reactions must be recorded on the patient's medical record.

The following actions may be required of the DTC after the evaluation of *serious or recurring adverse drug reactions* at its hospitals and clinics:

- Change formulary, if necessary, to obtain a drug of proven safety.
- Implement new prescribing procedures including restrictions and revise standard treatment guidelines if necessary.
- Modify patient monitoring procedures.
- Educate prescribing physician if needed.
- Educate other professional staff.
- Educate patient to reduce the possibility of ADR recurrence.
- Report to national drug authority and/or manufacturer, especially with regard to serious reactions, a new ADR or an unusual manifestation of a known ADR.

Monitoring of Adverse Drug Reactions by the DTC

DTCs should implement programs that track and report adverse drug reactions throughout the health care system. This program would include a system for monitoring drugs and vaccines. There are several methods to accomplish this and at minimum the following would be provided:

- Reporting of adverse drug reactions (including vaccines) to the DTC on standard forms (see Appendix 1)

- Analysis of ADR reports to include statistical analysis of prevalence, severity, and trends in the occurrence of ADRs

- Discussion and evaluation of reports by the DTC on a regular schedule (quarterly) and reporting to medical staff

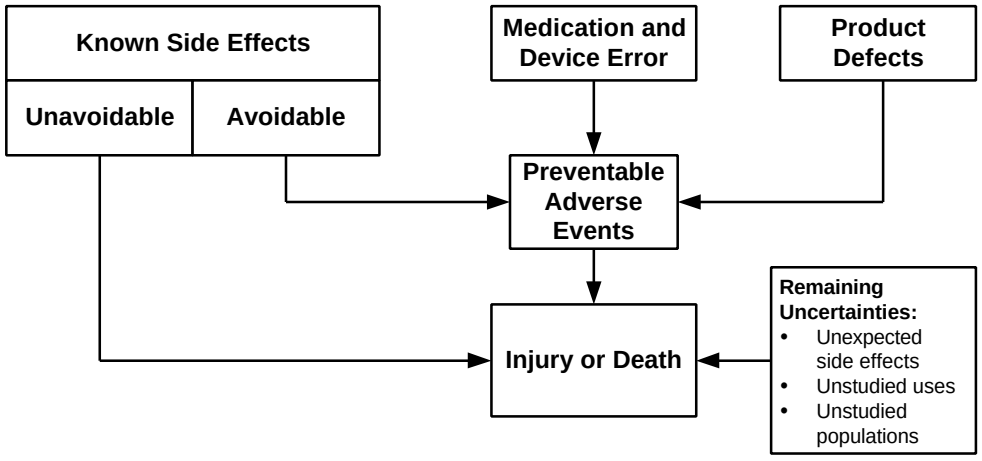
- Reporting to manufacturers and national regulatory authorities of severe and/or new or unusual reactions

Monitoring of ADRs should also include the review of the medication error and product quality reporting systems. These reporting and tracking systems are important as product quality and medication errors may have a significant effect on the occurrence of ADRs.

Prevention of Adverse Drug Reactions

Prevention of ADRs is possible and necessary. Without a prevention program, there will be many ADRs that occur needlessly, producing an increase in morbidity and associated health care cost. Many authorities agree that *over 50 percent of adverse drug reactions may be preventable.* There is a general lack of knowledge concerning ADRs, including the incidence, severity, and impact on health care. Most ADRs are related to the prescribing of an incorrect dose and to administration of a drug to a patient with a known allergy. The following schematic is illustrative of the factors that contribute to preventable adverse reactions.

Figure 1. Schematic of Preventable and Unavoidable Adverse Events



Preventing an adverse drug reaction can be enhanced by the practitioner by evaluating the following before prescribing a drug:

- Is this the correct drug for the patient's clinical condition?

- Is this the correct dose, route, and interval?

- Does the patient have any medical or physical conditions that would affect the pharmacokinetic aspects of the drug?

- Does the patient have an allergy to this medication or a chemically similar drug?

- Is the patient on another drug (or herbal product) that would cause a significant drug interaction?

- What is the patient's compliance with the medication?

- Is the drug being prescribed a "high-risk" drug for producing ADRs (for example, aminoglycosides, digoxin, warfarin, heparin, and antineoplastics)? Special precautions are necessary when using certain high-risk drugs.

- Is the drug being prescribed of high quality (reputable manufacturer, not expired, no deterioration)?

- Is the drug being administered correctly (sterile needle/syringe for injectable drugs, with food for GI irritants, etc.)?

The following actions by the DTC can help limit the occurrence of ADRs:

- Review ADR reports regularly and inform the professional staff of the incidence and impact of ADRs in the region.

- Discuss changes in the formulary or standard treatment guidelines for significant or recurring problems with adverse drug reactions.

- Educate staff, especially providers, concerning adverse drug reactions.

    - In-service education
    - Face-to-face education with providers
    - Drug information bulletins
    - Reports of collected adverse events

- Identify drugs on the formulary that are "high risk" and should be monitored closely by physicians and pharmacists. For example ¾

    - Aminoglycosides
    - Antineoplastics
    - Digoxin
    - Heparin
    - Warfarin

- Identify "high-risk" patient populations, including pregnant women, breastfeeding women, the elderly, children, and patients with renal or liver dysfunction; close monitoring of these patient populations by physicians and pharmacists will help prevent serious adverse reactions.

- Review medication errors and product quality complaints to ensure these are not contributing to the incidence of adverse drug reactions at the hospital.

ACTIVITIES

For activities in this session, the participants will break into groups of five individuals. A leader will be selected who will facilitate the discussion within the group. Active discussion within the groups is encouraged.

Activity 1. Penicillin Anaphylaxis Reported

As a member of a DTC that serves a network of 11 clinics and one hospital, you receive reports of an unusual number of adverse events associated with the use of Pronapen (penicillin procaine). These events are reported as allergic reactions to intramuscular injections of customary doses. The nursing assistants who administer the injections are alarmed and have refused to use this product. They are asking management to purchase any of the equivalent products (Despacilina, Scurocilina, and Bicilina) that have been used in the past.

The adverse event consists of the adult patient experiencing a feeling of impending doom, anxiety, or feeling "faint," requiring the person to lie down for a few minutes. The patient is usually pale and blood pressure tends to be normal or slightly high. Nurses quickly administer an injection of diphenhydramine intravenous or intramuscular. Ten to fifteen minutes later, the patient has recovered and is able to leave the clinic.

- How would you analyze this situation? What investigations would you carry out?

- What would you recommend to management regarding the procurement of an alternative or equivalent product?

- What would you communicate to the nursing staff and physicians?

Activity 2. Acute Respiratory Infection in a Two-Year-Old

A two-year-old patient and mother present at the clinic on 5/19/99 with a 48-hour history of fever, irritability, cough, and altered consciousness. Questioning of the mother reveals the following:

- 5/14/99—child was administered DPT and oral polio vaccine
- 5/15/99—child was seen with mild URI symptoms and treated with amoxicillin and cough syrup
- 5/17/99—onset of fever, irritability, altered consciousness
- 5/18/99—patient had been seen at health center and diagnosed with acute respiratory infection and treated with co-trimoxazole and paracetamol

Consider the following:

- What is the possibility of the patient having an adverse drug reaction in addition to the ARI?
- If you think it is an adverse drug reaction, which drug or drugs might be responsible? How did you arrive at this conclusion?
- What kind of action by the DTC is warranted in this case?

Activity 3. Phen-Fen

The combination drug phenteramine and fenfluramine was a popular diet drug throughout Europe and North America. Like all antiobesity drugs, this drug combination leads to tolerance after several months of use and weight gain invariably occurs when the drug is discontinued. But short-term effectiveness was dramatic, with countless success stories and many patients "demanding" prescriptions.

Safety of this combination was confirmed through the usual premarketing clinical trials. Because it was another weight control product, testing and evaluation were extensive and there was no "fast track" approval process.

Soon after marketing of the drug, spontaneous reports began to appear describing serious cardiovascular problems including valvular heart disease and pulmonary hypertension. Spontaneous reports continued until it became obvious that the drug combination was highly suspect for causing the adverse effect.

- What are some other possible causes for the cardiac conditions listed in the activity?
- What would have prevented this serious side effect from being detected in premarketing trials?
- Why would spontaneous reports be so effective in detecting this ADR after the drug's distribution to the general market?

Activity 4. Adverse Reaction to Acyclovir

A patient has sustained an adverse event related to the use of acyclovir. The report comes to you and there are additional requests from providers to switch from generic acyclovir to valacyclovir or the brand name Zovirax because of similar reports. The partially completed adverse drug reaction report for this patient is provided on page IV-18.

- Assess the probability of this reaction being caused by acyclovir. You may ask any questions of the instructor; he will represent the patient and the physician.

- How could this ADR have been prevented?

- What kinds of education might be the most effective in educating physicians about this drug or other drugs with similar side effects?

- Should this report be forwarded to the manufacturer or drug regulatory authority for review?

Figure 2. Activity 4 ADR Report

Patient and Reaction Information		**Comments**
Date	6/15/2000	
Name	M. Chaney	
Chart number	282882	
DOB	3/4/42	
Physician	Bernard	
Drug	Acyclovir	
Diagnosis for use	Herpes Simplex, Type II	
Dose	400 mg 3 times daily	
Date drug started	5/22/2000	
Date of reaction	5/26/2000	
Relevant medical history including concurrent drug therapy		
Description of ADR (use reverse if necessary)	1. Dizziness 2. Weakness 3. 4.	Symptoms lasted two days. Drug discontinued.
Outcomes attributed to ADR	1. None 2. 3. 4.	
Probability of reaction	Naranjo Score:	
Severity code	Severe Moderate XX Minor Incidental	
DTC action Mark patient's chart Discuss with prescriber Add to database Report to NDA Report to manufacturer	 Yes No Yes No Yes No Yes No Yes No	
Reported initiated by: Date		

SUMMARY

Drug safety issues are critical to a health care system. The DTC is in a position to have a significant impact on preventing and managing these problems. The DTC should have appropriate people to assess the literature carefully to determine the safety of drugs for the formulary. Appropriate management of adverse drug reactions should include ¾

- Implementing systems to monitor the occurrence of reactions
- Evaluating suspected ADRs
- Reporting ADRs to regulatory authorities and manufacturers
- Assessing safety issues of new drugs in formulary management
- Managing spontaneous reports
- Preventing the occurrence of adverse drug reactions by ¾
    - Monitoring the health care system through ADR reporting
    - Carefully evaluating patients before prescribing medications, especially high-risk patients or patients on high-risk drugs
    - Educating staff, especially providers, concerning adverse drug reactions

Appendix 1. Adverse Drug Reaction Reporting Form

(for hospital and primary care clinic use only)

Patient and Reaction Information		**Comments**
Date		
Name		
Chart number		
DOB		
Physician		
Drug		
Diagnosis for use (Indications)		
Dose		
Date drug started		
Date of reaction		
Relevant medical history including concurrent drug therapy		
Description of ADR (use reverse is necessary)	1. 2. 3. 4.	
Outcomes attributed to ADR	1. 2. 3. 4.	
Probability of reaction	Naranjo Score:	
Severity code	Severe Moderate Minor Incidental	
DTC action Mark patient's chart Discuss with prescriber Add to database Report to NDA Report to manufacturer	 Yes No Yes No Yes No Yes No Yes No	
Reported initiated by: Date		

Severity Assessment Guide

Severity of Adverse Drug Reaction	**Description**
Severe	Fatal or life threatening
Moderate	Requires antidote, medical procedure, or hospitalization
Mild	Symptoms are evident and require only the discontinuation of drug therapy
Incidental	Very mild symptoms; patient is given option to continue or discontinue

Appendix 2. Naranjo Algorithm for Assessing Probability of an ADR Occurrence

Question	Yes	No	Do Not Know
Are there previous conclusive reports on this reaction?	+1	0	0
Did the adverse event appear after the suspected drug was administered?	+2	-1	0
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
Did the adverse reaction reappear when the drug was readministered?	+2	-1	0
Are there alternate causes (other than the drug) that could solely have caused the reaction?	-1	+2	0
Was the drug detected in the blood (or other fluids) in a concentration known to be toxic?	+1	0	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by objective evidence?	+1	0	0

The total score is calculated from the table-defined category an adverse reaction belongs to. The categories are defined as follows:

Definite	> 9
Probable	5–8
Possible	1–4
Doubtful	0